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Applicants : Mouritsen et al.

Serial No. : 08/955,373

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Examiner : Ron Schadron

Art Unit : 1644

For : **INDUCING ANTIBODY RESPONSE AGAINST SELF-PROTEINS WITH THE AID OF FOREIGN T-CELL EPITOPES**

745 Fifth Avenue, New York, New York 10151

DECLARATION OF ROLF M. ZINKERNAGEL, PhD

Assistant Commissioner for Patents
Washington, D.C. 20231
Dear Sir:

ROLF M. ZINKERNAGEL declares and says that:

1. I am familiar with the subject matter of the above-captioned application (the present application) as: I am informed that a concurrently-filed Amendment presents claims as reproduced below or substantially as reproduced below, after my signature, which I have read and understood; I have been informed that the Examiner has indicated that Dr. Paul Travers - a previous declarant in the present application - is not a person knowledgeable in the field of immunology or more specifically in the field relating to immunosuppression; and I have been informed that the Examiner, in rejecting claims, has indicated that it would have been obvious for an immunologist to substitute suppressor epitopes in self-proteins with foreign T-helper epitopes or that an immunologist could have substituted suppressor epitopes in self proteins with T-helper epitopes. My *Curriculum vitae*, which is publicly available at *inter alia* http://www.nobel.se/medicine/laureates/1996/zinkernagel-cv.html , is attached and incorporated herein by reference. Among other accomplishments, I was awarded the Nobel Prize in Physiology or Medicine with Peter C. Doherty, PhD, in 1996, for our discoveries in concerning the specificity of the cell mediated immune defense. Accordingly, I respectfully submit that I am well qualified to speak as to the present application and Dr. Travers' qualifications.

DR. TRAVERS IS WELL KNOWN AS BEING QUITE KNOWLEDGEABLE IN THE FIELD OF IMMUNOLOGY AND IN THE FIELD OF IMMUNOSUPPRESSION

2. As mentioned above, I am informed that the Examiner has indicated that Dr. Paul Travers is not a person knowledgeable in the field of immunology, or more specifically, in the field relating to immunosuppression. I respectfully disagree with the Examiner's opinion of Dr. Paul Travers.

3. Dr. Paul Travers is the prominent author of the preeminent textbook Janeway/Travers Immunology. This textbook is probably the most widely known and recognized textbook in immunology in the world. Hence, Dr. Paul Travers is an internationally acknowledged and recognized immunologist. Dr. Travers, in my opinion, has a profound knowledge of the basic functioning of the immune system, especially as reflected by Dr. Travers being the prominent author of the preeminent textbook Janeway/Travers Immunology – again probably the most widely known and recognized textbook in immunology in the entire world.

4. Accordingly, I respectfully submit that no one in the field of immunology would or could reasonably concur with the Examiner's opinion that Dr. Paul Travers is not a person knowledgeable in the field of immunology, or more specifically, in the field relating to immunosuppression; and, I respectfully disagree with this opinion of Dr. Paul Travers by the Examiner.

THE EXAMINER'S HYPOTHETICAL SUBSTITUTION OF SUPPRESSOR EPITOPES IS NOT AND WAS NOT POSSIBLE

5. I am also informed that the Examiner has indicated that it would have been obvious for an immunologist to substitute supressor epitopes in self-proteins with foreign T-helper epitopes. As a person clearly skilled in the field of immunology, and indeed recognized as an expert in the field of immunology, I respectfully submit, based on my education, training and experience, that the Examiner's hypothetical substitution of suppressor epitopes in self-proteins with foreign T-helper epitopes, is today not possible, and was not possible at the August 26, 1993 effective filing date of the present application; and therefore, that it could not have been obvious for an immunologist to substitute suppressor epitopes in self-proteins with foreign T-helper epitopes.

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6. Simply, as a person clearly skilled in the field of immunology, and indeed recognized as an expert in the field of immunology, based on my education, training and experience, I fail to see how the Examiner's hypothetical substitution of suppressor epitopes could be possible today or could have been possible at the August 26, 1993 effective filing date of the present application. Even today, it is highly controversial whether there exists such a thing as supressor epitopes; but, more importantly, there is, to the best of my knowledge, no known method of positively identifying such suppressor epitopes. And at the August 26, 1993 effective filing date of the present application, to the best of my knowledge, there was no known method of positively identifying such suppressor epitopes. Consequently it is not possible today – and was not possible at the August 26, 1993 effective filing date of the present application - to devise any strategy for substituting supressor epitopes with foreign T-helper epitopes. Clearly, if one skilled in the art could not and cannot positively identify suppressor epitopes in self-proteins (whose existence is still a matter of debate in the art), based on my education, training and experience, there is no way and was no way for the skilled artisan to perform the hypothetical substitution postulated by the Examiner.

7. Thus, it was not obvious and is not obvious for an immunologist to substitute suppressor epitopes in self-proteins with foreign T-helper epitopes, contrary to the Examiner's hypothesis that it would have been obvious to substitute suppressor epitopes in self-proteins with foreign T-helper epitopes, with which, based on my education, training and experience, I respectfully disagree.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated: Zurich 8-May 02 By: R. Zinkernagel
ROLF M. ZINKERNAGEL, PHD

CLAIMS UNDERSTOOD TO BE ADDED OR SUBSTANTIALLY ADDED

--56. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that

animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein;

whereby, the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

57. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

58. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving

tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

59. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

60. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

61. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

62. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

63. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

64. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

65. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving

secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

66. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

67. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

68. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

69. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

70. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

a. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein;

whereby, the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

b. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

c. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

d. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

e. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier

protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

f. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

g. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

h. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution

preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

i. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

j. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

k. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

l. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

m. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

n. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken.

71. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, inducing antibody production in the animal against the self-protein of that animal, and eliciting an immune response in the animal which includes an MHC class II immune response as to an immunodominant T-cell epitope which is foreign to the animal and an

autoantibody response in other MHC-haplotypes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

a. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing the immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or

b. the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing the immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken.

72. (New) A method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, wherein:

a. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide

containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein;

whereby, the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

b. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

c. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

d. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide

containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

e. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

f. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

g. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

h. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

i. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least ten amino acids on each side of the peptide fragment;

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

j. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least fifteen amino acids on each side of the peptide fragment,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

k. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken; or,

l. the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein; and,

the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein,

whereby the modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

m. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken; or,

n. preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, and B-cell autotolerance to the self-protein is broken.

73. (New) The method of any one of claims 56-72 wherein the modified self-protein is a recombinant modified self-protein.

74. (New) The method of any one of claims 56-72 wherein the self-protein is tumor necrosis factor alpha (TNF-α), tumor nucrosis factor beta (TNF-β), gamma interferon (γ-interferon), interleukin 1 (IL-1) or immune globulin (IgE).

75. (New) The method of claim 73 wherein the self-protein is tumor necrosis factor alpha (TNF-α), tumor nucrosis factor beta (TNF-β), gamma interferon (γ-interferon), interleukin 1 (IL-1) or immune globulin (IgE).

76. (New) The method of any one of claims 56-72 wherein the administering includes administering an adjuvant.

77. (New) The method of claim 76 wherein the adjuvant comprises calcium phosphate, saponin, quil A or a biodegradable polymer.

78. (New) The method of claim 73 wherein the administering includes an adjuvant.

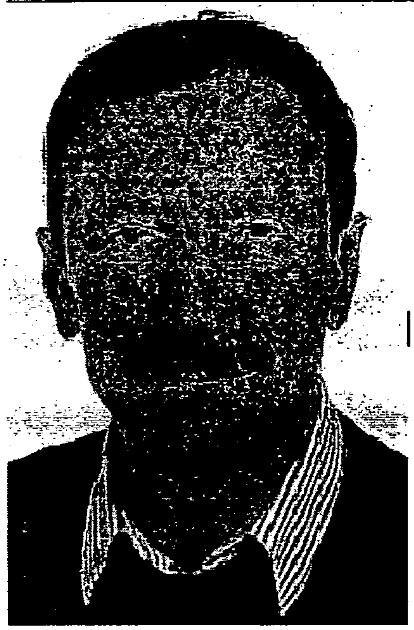
79. (New) The method of claim 75 wherein the administering includes an adjuvant.--

Department of **Pathology**

Institute of Experimenal Immunology

curriculum vitae

Rolf M. Zinkernagel



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Education

1962	Mathematisch-Naturwissenschaftliches Gymnasium, Basel, Matura
1962–1968	Faculty of Medicine, University of Basel
1967–1968	Course in Tropical Medicine, Tropical Institute, University of Basel
1968	National Board Examination
1968	E.C.F.M.G. (USA)
1970	M.D. Thesis
1971	Postgraduate course in Experimental Medicine, Faculty of Medicine, University of Zürich
1975	Ph.D.Thesis, Australian National University, Canberra, Australia

Professional Record
1966 Externship, Glen Cove Community Hospital, Glen Cove, Long Island, N.Y., USA
1969 Internship, Surgical Department, Clara-Spital, affiliated to the Facility of Medicine, University of Basel
1969 – 1970 Postdoctoral Fellow, Laboratory for Electron

Microscopy, Institute of Anatomy, University of Basel
1971 – 1973 Postdoctoral Fellow, Institute of Biochemistry, University of Lausanne, Switzerland
1973 – 1975 Visiting Fellow, Department of Microbiology, The John Curtin School of Medical Research, Australian, National University, Canberra, Australia
1975 – 1976 Associate (Assistant Professor), Department of Immunopathology, Research Institute of Scripps Clinic, La Jolla, California
1976 – 1979 Associate Member (Associate Professor), Department of Immunopathology, Scripps Clinic and Research Foundation, La Jolla, California
1977 – 1979 Adjunct Associate Professor, Department of Pathology, UCSD
1979 Member (Full Professor), Department of Immunopathology, Scripps Clinic and Research Foundation
1979 – 1988 Associate Professor, Department of Pathology, University of Zürich, University Hospital, Zürich
1988 – 1992 Full Professor, Department of Pathology, University of Zürich, University Hospital, Zürich
1992 – Head, Institute of Experimental Immunology, Zürich

Honorary and Professional Organizations
1971 – Swiss Society of Allergy and Immunology (President 1993 – 1994, Honorary member 1996)
1973 – 1975 Australian Society for Immunology (Honorary member 1996)
1977 – American Association of Immunologists (Honorary member 1993)
1977 – American Association of Pathologists
1978 – Scandinavian Society of Immunology (Honorary member 1978)
1980 – Société Française d'Immunologie (Honorary member 1980)
1980 – Swiss Society of Microbiology
1981 – Swiss Society of Pathology
1984 – EMBO European Molecular Biology Organization
1987 – Swiss Association for the Study of the Liver
1989 – Swiss Society of Cell and Molecular Biology
1989 – Academia Europea
1990 – Gesellschaft für Immunologie
1990 – International Society for Antiviral Research
1990 – ENI European Network of Immunological Institutions
1990 – Deutsche Gesellschaft für Virologie
1991 – Deutsche Gesellschaft für Immunologie
1992 – The Delphinium Society
1994 – Schweizerische Akademie der Medizinischen Wissenschaften
1994 – Deutsche Akademie der Naturforscher Leopoldina
1996 – American Academy of Microbiology, Fellow
1996 – US National Academy of Sciences, Foreign Fellow
1996 – Australian Academy of Sciences, Foreign Fellow
1998 – American Academy of Arts and Sciences, Foreign Fellow
1998 – Royal Society, Foreign Fellow
1998 – Academie Royale de Medicine de Belgique, Foreign Fellow
1998 – Berlin-Brandenburgische Akademie der Wissenschaften
1998 – Foundation Gen Suisse
1998 – WIF World Innovation Foundation, Honorary Member
1998 – ECEAR European Conference on Experimental AIDS Research
1999 – FMH Verband der Schweizer Ärzte und Ärztinnen
2000 – Schweizer Wissenschafts- und Technologierat
2001 – Patronage Committee Foundation Swiss Bridge

Editorial Board
1976 – 1988 Experimental Cell Biology
1977 – Immunogenetics
1978 – 1984 Parasite Immunology

1978 – 1980 Journal of Immunology
1979 – 1989 Thymus
1980 – Zeitschrift für Immunologie-Immunobiology
1980 – 1988 Antiviral Research
1981 – European Journal of Immunology (Executive Committee 1994)
1981 – Journal of Environmental Pathology Toxicology & Oncology
1981 – 1984 Journal of Experimental Medicine
1981 – 1983 Current Topics in Microbiology and Immunology
1982 – Scandinavian Journal of Immunology
1983 – Cellular Immunology
1983 – International Journal of Microbiology
1987 – 1989 Europ.Molecular Biology Organization Journal
1987 – European Journal of Clinical Investigation
1988 – 1991 Journal of Autoimmunity
1988 – 1991 Clinical Immunology and Immunopathology
1988 – International Immunology
1988 – 2000 Urologia Internationalis
1989 – Annual Review of Immunology
1991 – International Review of Experimental Pathology
1991 – International Journal of Clinical & Laboratory Research
1992 – Immunology today
1992 – Immunology and Cell Biology
1994 – Immunity
1994 – Viral Immunology
1994 – 2000 Virology
1995 – Immunological Reviews
1996 – Cell and Tissue Research
1997 – Seminars in Immunopathology
1997 – Current Opinion in Microbiology
1998 – International Journal of Molecular Medicine
1998 – History and Philosophy of the Life Sciences
2000 – Cytokine

Honours
1981 Cloëtta Stiftung (Zürich)
1982 Jung Stiftung (Hamburg)
1983 Paul Ehrlich Preis (Frankfurt)
1985 Mack-Forster Preis (Europ.Ass.Clin.Inv.)
1986 Gairdner Foundation (Toronto)
1987 Institute for Cancer Research (New York)
1988 Louis Jeantet Foundation (Geneva)
1988 Naegeli Stiftung (Zürich)
1992 Christoforo Colombo Award (Genova)
1995 Lasker Award (New York)
1996 Honorary Dr. h.c., University of Liège
1996 Honorary Dr. h.c., Australian National University, Canberra
1996 Nobel Prize for Medicine or Physiology
1997 Honorary Dr. h.c., University of Oslo
1997 Honorary Dr. h.c., University of Quebec
1997 Honorary Dr. h.c., University of Genova
1997 Drew-Novartis Award
1997 Reichstein Medaille (Zürich)
1998 Honorary Dr. h.c., Latvian University, Riga
1998 Honorary Dr. h.c., Agricultural University of Warsaw
1999 Honorary Companion in the General Division of The Order of Australia
1999 Member of the Order pour le mérite for Sciences and Arts (Germany)
1999 Honorary Dr. h.c., University of Basel, Switzerland
2000 Honorary Dr. h.c., University of Montréal, Canada
2000 Honorary Dr. h.c., University of Buenos Aires, Argentina
2000 Honorary Dr. h.c., Medical Academy of the University of Warsaw
2000 Honorary Dr. h.c., Medical University of Odessa

Scientific Advisory Board
1977 – Temporary Adviser National Science Foundation

Washington
1979 – 1980 Study section NIH Virology
1980 NIH-Task Force Immunology
1981 – 1983 Gutachter Sonderforschungsbereich 107 «Vollzugsmechanismus der Immunreaktion», Mainz, DFG
1981 – 1983 Ministère de la recherche et de l'Industrie Action «Régulations en Immunologie et Immunopathologie» Paris
1982 – 1983 Schwerpunktprogramm Histokompatibilitätsgen-komplex Deutsche Forschungsgemeinschaft
1982 – 1986 Basel Institut für Immunologie, Swiss Scientific Advisory Board
1982 – 1991 Zentrum für Lehre und Forschung, Universität Basel, Advisory Board
1985 – 1989 Scientific Advising Group of Experts in Vaccine Development WHO
1986 – 1991 Scientific Advisory Board, Max Planck-Institute for Biology, Tübingen
1986 – 1988 Biogen, Advisor
1988 – Cancer Research Institute (Scientific Advisory Council)
1988 – Sandoz Prize for Immunology Committee
1989 – Schweiz. Institut für Allergie und Asthmaforschung, Davos
1989 – Academia Europaea, London
1990 – 1992 Founding Committee Max Planck - Institute of Infectiology
1991 – Scuola Superiore d'Immunologia, Napoli
1991 – 1993 EMBO Council
1992 – 1996 Biozentrum der Universität Basel
1992 – 2000 Marcel Benoist Preis Kommittee
1992 – Universität Basel, Biozentrum
1996 – 2000 Jung-Stiftung für Wissenschaft und Forschung, Hamburg (Committee member)
1997 – Fondation pour le Recherche sur le Vieillissement, Genève
1998 – 2000 Zurich University Association
1998 – Foundation Science et Cité, Bern
1998 – 2000 WIF World Innovation Foundation, Huddersfield GB
1998 – Swiss Bridge Foundation, Zürich
1999 – Academy of Cancer Immunology, New York
1999 – Biomedical Research and Study Centre, Riga
1999 – SFO - Foundation to support Organ Donation, Zürich

Special lectures
1979 The Kinyoun Lecture NIH
1980 Wellcome visiting Professorship, Denver
1980 Special University of London Lecture
1982 Campbell Memorial Lecture, Asilomar
1983 A. v. Graefe Lecture, Berlin
1983 Armauer Hansen Memorial Lecture, Addis Abeba
1993 Grabar Lecture, French Society of Immunology
1994 Harvey Lecture, New York
1986 Peter Gorer Lecture, British Society of Immunology
1997 Felix-Hoppe-Seyler Lecture
1997 Landsteiner Lecture, Frankfurt
1998 Hubert-Bloch Lecture, Basel
1998 Leopold G. Koss Lecture, Bern
1998 Wolfgang-Pauli Lecture, Zürich
2000 Meyenburg Lecture, Heidelberg

Department of Pathology

Institute of Experimental Immunology

Bibliography Rolf Zinkernagel

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6. Zinkernagel, R.M. and Doherty, P.C.
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8. Zinkernagel, R.M., Blanden, R.V., and Langman, R.E.
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10. Zinkernagel, R.M. and Doherty, P.C.
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